

Pancreatic Blastomatous Tumor in a Child Responding to Therapy Used for Hepatoblastoma: Case Report and Review of the Literature

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A case is reported of a 7-year-old girl diagnosed with initially inoperable metastatic embryonic pancreatic tumor, which showed a significant clinical response to chemotherapeutic agents commonly used to treat hepatoblastoma. This regimen was selected because certain histologic features of the tumor demonstrated characteristics seen in hepatic tissue. After two courses of chemotherapy (cis-platinum and adriamycin), there

was a significant reduction of the primary mass, and it was completely resected, although the tumor subsequently recurred in the metastatic, unoperated site. The embryologic relationship between the tumor in this patient and hepatoblastoma, as well as the literature concerning treatment in pediatric pancreatoblastic tumors are reviewed. Complete eradication of tumor appears to be necessary for cure. © 1996 Wiley-Liss, Inc.

Key words: pancreatoblastoma, pancreatic tumors, pediatric oncology, chemotherapy, embryology

INTRODUCTION

Pancreatoblastoma is a rare tumor of childhood of uncertain histogenesis [1,2]. Literature on this tumor is scant, mostly consisting of isolated case reports or small series, and primary modalities of therapy utilized are surgical resection and/or radiation therapy [2-11]. A case is presented of an inoperable blastomatous abdominal tumor in a 7-year-old girl arising in the pancreas and differing in some histologic respects from pancreatoblastoma. Treatment for hepatoblastoma (HBL) was used because of similar histologic features in this tumor with a good initial response.

CASE REPORT

The patient is a previously healthy 7-year-old white female who presented with a left upper quadrant abdominal mass. There was no history of fever, unusual bruising or bleeding, or bone pain. There was a history of slightly decreased appetite and possible weight loss. Review of systems was otherwise unremarkable. Her past medical history was noncontributory. She was on no medications, ate a "balanced" diet, and was developmentally appropriate. Her family history was notable for aplastic anemia in a paternal great-grandfather at age 50, breast cancer in a maternal aunt, and a "blood-clotting" disorder in a maternal grandmother and great-grandfather. At the time of referral, the patient appeared comfortable; her temperature was 36.8°C, heart rate 100/min, respiratory rate 20/

min, and blood pressure 100/70 mm Hg. Her head and neck exam was unremarkable. Her chest was clear with decreased breath sounds at the left base. Cardiovascular examination was unremarkable. Examination of her abdomen revealed a 10 × 15 cm firm, nontender mass in the left upper quadrant. Her extremities were normal, neurological examination was intact, and she had normal Tanner stage I genitalia.

Laboratory examination demonstrated a hemoglobin of 11.3 g/dL (11.5-15.5), hematocrit of 34.1% (35.0-45.0), platelet count of 335,000/cu mm (150-450), and white blood cell count 7,200/cu mm (4.5-13.5). The differential was 50% polymorphonuclear neutrophils, 13% band forms, 27% lymphocytes, 6% atypical lymphocytes, and 4% eosinophils. Her BUN was 8 mg/dL [7-18], and creatinine was 0.6 mg/dL (0.3-0.8). Her serum calcium was 9.3 mg/dL (8.8-10.8), LDH 895 U/L (163-304), SGOT 27 U/L (8-42), SGPT 7 U/L (3-36 mg/dL), bilirubin (total/direct) 0.3/0.1 mg/dL (0.2-1.0/<0.3), and uric acid 6.5 mg/dL (2.0-6.0). Urinalysis demonstrated a specific gravity of 1.015, pH of 7.5, 2+ occult blood and trace protein. Microscopic examination

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showed 90–100 RBCs/HPF, 0–1 WBCs/HPF, 10–12 epithelial cells/HPF, and few bacteria. An alpha-fetoprotein (AFP) level was 82,940 ng/mL (normal values 0–8.5). Bone marrow examination demonstrated mild erythroid hyperplasia but was otherwise normal. A bone scan demonstrated no evidence of bony involvement. A CT scan and MRI of the abdomen showed a large leftsided retroperitoneal mass measuring 13 cm in its greatest diameter that appeared separate from the liver, spleen and kidney, although contiguity with the caudate lobe of the liver could not be totally excluded. The tail of the pancreas was not well visualized. Two lucent lesions were seen in the right lobe of the liver and were felt to represent metastases. A CT scan of the chest revealed no evidence of metastases.

The patient went to surgery for exploratory laparotomy and possible resection. Intraoperatively, she was noted to have a firm, fungating mass involving the pancreas, stomach, left kidney, spleen, adjacent retroperitoneum, and inferior vena cava. The mass was felt to be unresectable and was biopsied only. Postoperatively, she was managed with intravenous hydration, alkalization, and allopurinol.

The initial pathologic diagnosis of the tumor was pancreatoblastoma vs. adenocarcinoma of the pancreas (detailed discussion of the findings below). However, certain features of the tumor were suggestive of hepatic origin, and hepatoblastoma was included in the differential diagnosis. Treatment was initiated based on therapy used for adult pancreatic carcinoma and consisted of a course of external beam irradiation with concomitant fluorouracil (5-FU) 500 mg/m²/d as a short IV infusion for 3 days at the beginning of radiation for sensitization. She received a total of 2,340 cGy divided into 13 fractions of a planned course of 4,000–5,000 cGy but had no significant decrease in the size of the mass clinically or radiologically despite a decrease in AFP from 67,305 ng/mL immediately prior to radiation to 8,532 ng/mL.

Because of the hepatoid features of the mass, the impression of an outside consultant (Dr. Juan Rosai, whose help we gratefully acknowledge), that the tumor was of liver cell origin, the poor clinical response to radiation therapy, and the dismal prognosis of pancreatic adenocarcinoma, radiation therapy was discontinued and the patient was started on a protocol successfully used for HBL in children. This therapy, consisting of, every 3rd week, courses of cis-platinum (CDDP) and Adriamycin (doxorubicin) (ADR) (90 mg/M² of cis-platinum (CDDP) administered intravenously over 8 hours, followed by a 4-day infusion of Adriamycin at a dose of 20 mg/M²/day) was initiated within 1 week of termination of radiation therapy.

After receiving two courses of this chemotherapy, a CT of the abdomen demonstrated marked reduction of the primary mass (7 cm in greatest diameter) with evidence

of necrosis within the mass and complete resolution of liver metastasis. AFP levels fell from a pre-CDDP-ADR level of 8,532 ng/mL to 330 ng/mL. She underwent a second laparotomy and distal pancreatectomy, splenectomy, left nephrectomy, and left adrenalectomy. The primary mass was completely excised, and the margins of resection were free of tumor. Approximately 10 days after surgery, her alpha-fetoprotein level was <5.0 ng/mL; follow-up CT scans of the chest and abdomen 3 weeks later demonstrated no residual or metastatic neoplasm. The patient received an additional three courses of this chemotherapy after which she manifested ototoxicity and nephrotoxicity. No cardiotoxicity was noted. Her therapy was then changed to a regimen of multiple courses of vincristine and 5-FU (vincristine 1.5 mg/M² IV, 5-FU 500 mg/M²/day × 3 days) since initial partial response to 5FU could not be excluded.

Approximately five months after resection, a CT scan done to evaluate abdominal pain demonstrated a new mass in the operative bed. At this point, the patient had received one course of the vincristine/5-FU regimen, as well as one additional dose of vincristine. Findings at laparotomy included calcified greater omental masses and a 2 × 3 cm calcified mass in the greater curvature of the stomach. The liver, right kidney, and remainder of the stomach were normal. Pathologic examination revealed that these represented areas of fat necrosis and suture granulomas; no tumor was identified. Four additional courses of vincristine and 5-FU were administered to complete an arbitrary 6 months of therapy.

The patient did well and remained disease-free for ~2 months after discontinuing chemotherapy (~7 months after tumor resection). At that time, she suffered tumor recurrence in the liver at the site of initial metastatic disease. She had a partial response to carboplatin and etoposide (VP 16) and underwent wedge resection of tumor in the liver along with a lymph node in the porta hepatis, which was infiltrated by tumor. She subsequently developed rapidly progressive tumor in the liver, which was nonresponsive to further chemotherapy and expired 18 months after diagnosis. Postmortem examination was not performed.

MATERIALS AND METHODS

Both the biopsy tissue and the surgical specimen obtained subsequently were processed in the same manner. Tissues were fixed in 10% buffer formalin or B-5 fixative.

Paraffin-embedded tissue blocks were cut at 5 μm thickness and stained by conventional histologic technique with hematoxylin and eosin (H/E), Gomori's reticulum, and Masson's trichrome. For immunohistochemistry, an avidin-biotin complex immunoperoxidase-linked detection kit was used following the manufacturers' in-

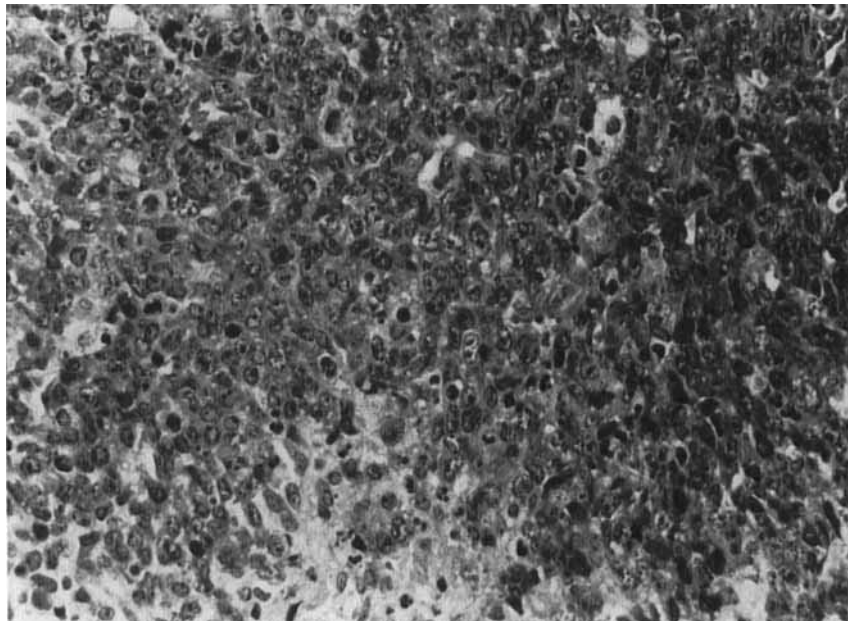


Fig. 1. Solid area of the tumor showing cohesive epithelial cells with occasional interspersing of macrophages (hematoxylin/eosin, $\times 225$).

structions (Vectastain ABC kit, Vector Laboratories, Burlingame, CA). The primary antibodies were commercially available antibodies against alpha-1-fetoprotein, alpha-1-antichymotrypsin, albumin, amylase, fibrinogen and neuron-specific enolase (Dako, Santa Barbara, CA); antimacrophage antibody HAM 56 (Enzo Biochem, New York, NY); chromogranin A (Boehringer Mannheim, Indianapolis IN); and pancreatic polypeptide. For electron microscopy, tissue was minced in 3% glutaraldehyde, postfixes in osmium tetroxide, dehydrated, and embedded in Spurr's plastic according to standard technique. Ultrathin sections stained with uranyl acetate and lead citrate were examined with a Zeiss 10-A electron microscope.

PATHOLOGY

The histopathology of the initial biopsy specimen showed highly mitotic epithelial cells in cohesive masses, amidst which macrophages appeared irregularly interspersed (Fig. 1). A second pattern observed was composed of tracts or trabeculae of cells, of various widths, separated by sinusoidal-like spaces lined by endothelial cells. This pattern was closely reminiscent of hepatoblastoma, particularly of the "macrotrabecular type"¹, in which the tumor cells tend to be arranged in trabeculae many cells thick (Fig. 2). However, the hepatocellular origin of the neoplasm could not be established by histologic methods, as the tumor cells were negative for albumin and fibrinogen immunostaining. Lack of immunore-

activity was also noted to antibodies directed against pancreatic polypeptide, amylase (which stained some normal pancreatic acini entrapped within the tumor), chromogranin, neuronal-specific enolase, vimentin, and leukocyte common antigen. Few individual cells were positive for alpha-1-antitrypsin and alpha-1-fetoprotein. Antimacrophage antibody (HAM 56) stained the macrophages in the areas of "starry-sky" pattern, but the tumor cells were negative. Cytokeratin stains were intensely positive (Fig. 3).

The operative specimen obtained 3 months after initial biopsy consisted of a $15 \times 9.5 \times 8.5$ cm. mass arising within the body and tail of the pancreas and growing outward to attach to the spleen, left kidney, left adrenal, and neighboring omentum. These organs were surgically resected en bloc with the tumor and were found to be intimately bound by fibrous tissue to the neoplasm without parenchymal replacement by tumor. Lymph nodes within the omentum showed lesions compatible with posttherapy tumor destruction. Approximately 80% of the tumor tissue showed the effects of therapy in the form of scarring, hyalinized stroma, tumor necrosis, and groups of "scavenger" cells (foamy histiocytes amid scarred stroma). The remaining, apparently viable tumor tissue retained the histologic appearance of solid cellular masses, as previously described. Some areas of residual tumor showed a distinctly tubular arrangement, with a central lumen bordered by neoplastic epithelial cells.

Electron microscopy study disclosed a very complex subcellular structure of the tumor cells. These were rich

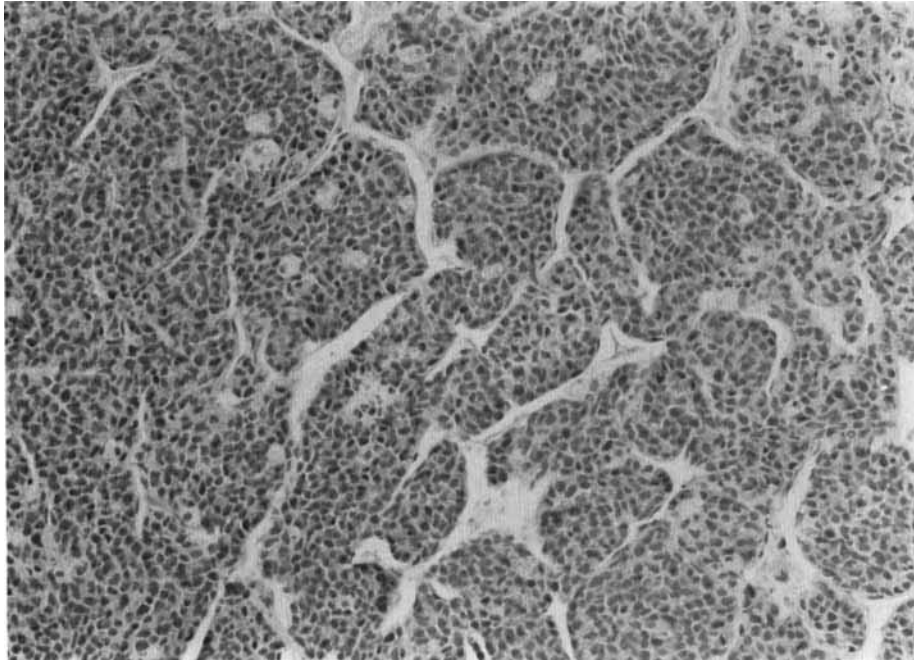


Fig. 2. Tumor cells are arranged in trabeculae separated by sinusoidal spaces, in a pattern reminiscent of hepatoblastoma (negative immunostaining for albumin, hematoxylin counterstain, $\times 125$).

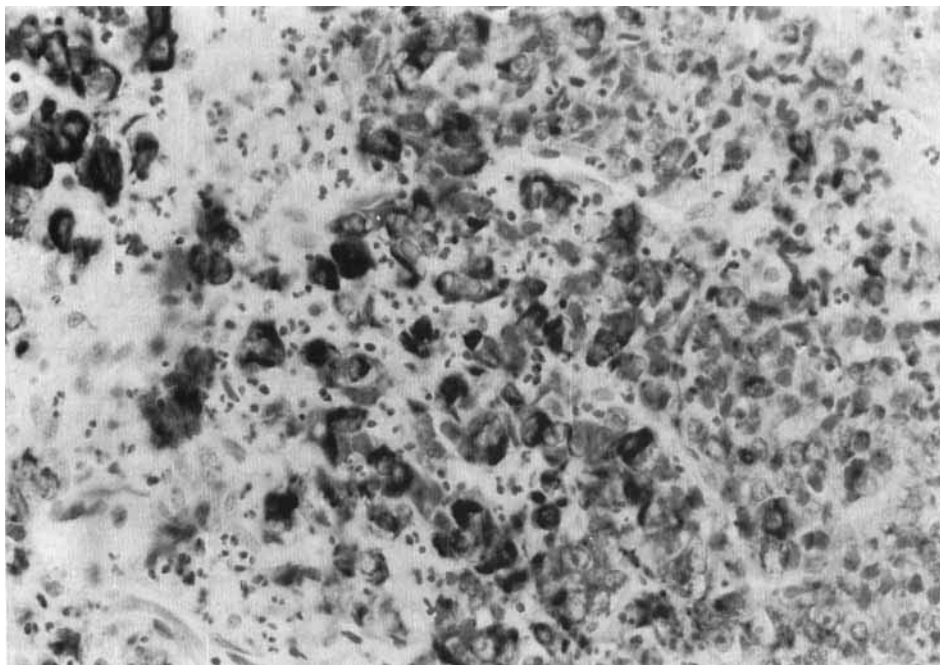


Fig. 3. Tumor cells demonstrate intense cytoplasmic positivity for cytokeratin (anti-cytokeratin immunostain, hematoxylin counterstain, $\times 125$).

in organelles, showing well-developed, rough endoplasmic reticulum, mitochondria of light matrix that usually contained one to four small, dense mitochondrial inclusions, few lysosomes, and profiles of Golgi apparatus.

No glycogen pools were seen, but some cells contained lipid droplets. Of interest was the presence (in many cells) of formation of canalicular spaces with a distinct microvillus border. This was noted in cells lying individ-

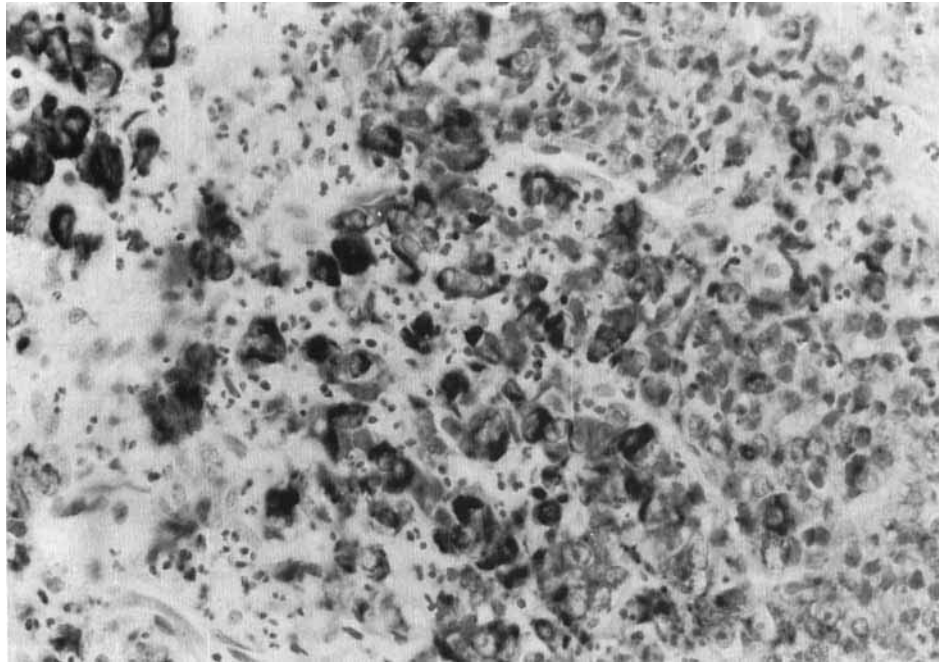


Fig. 4. Detail of a canalicular structure, showing well-developed microvilli and tight junctions (arrows) between opposing cells ($\times 20,000$).

ually, or at sites of cell-to-cell apposition. In the later case, it was not uncommon to observe the presence of tight junctions between cells bordering a canaliculus (Fig. 4).

DISCUSSION

Malignant pancreatic tumors are very rare in children. Pancreatoblastoma is histologically distinct from typical ductal or acinar pancreatic adenocarcinoma [1]. Because of their varieties, it may be that the morphologic spectrum of these neoplasms is incompletely known. With the reservations explained earlier, we approached this patient's management using therapy appropriate for HBL. Making accurate statements regarding prognosis in a tumor this rare is difficult, but there are data to suggest that surgical resection is more likely to be successful in pancreatoblastoma than in adult pancreatic carcinoma. In adults, only 13% of these tumors are resectable at presentation, and median survival postresection is 14–17 months [12]. Camprodon and Quintenilla [9] reviewed 28 cases of childhood pancreatic malignancy reported between 1885 and 1981 and noted that resection was possible in 12 (40%) of these cases. Follow-up information was obtainable for seven of those patients; all were alive a minimum of 5 years after surgery, with survival times ranging from 5 to 20 years. Nagaraj and Polk [3] report an overall survival rate of 80% in 20 children with resected pancreatoblastoma/pancreatic carcinoma of the infantile type.

Other reviews paint a less optimistic picture. Tsukimoto et al. [10] reviewed 12 cases from the Japanese literature; surgery was impossible in three patients, six had a laparotomy only, and two had pancreaticoduodenectomy performed. All died within 6 months of the onset of symptoms. Taxy reviewed 16 cases; in 14 where follow-up was available, only three had survived 9 months or longer [11].

There are several case reports in the literature indicating responses to chemotherapy, most notably to regimens containing CPDD. These are summarized in Table I [7,13–18, M. Kletzel, pers. comm.]. Notably, the only patients surviving received chemotherapy followed by total surgical resection or surgical resection with microscopic residual followed by aggressive radiation therapy or high dose chemotherapy with autologous marrow rescue.

Comparing responses to other therapeutic modalities in adult and pediatric pancreatic malignancy is difficult because of the low incidence of this disease in childhood. Moreover, pancreatic tumors in adults and children are histologically different entities. In adults, radiation therapy plays a significant role in palliation and may improve survival [12]. Griffin [4] reported successful control of locally recurrent pancreatoblastoma with radiation therapy. Chemotherapy in adult disease has failed to be of any benefit in disease control or improvement of survival [7]. Iseki et al. [7] reported control of metastatic pancreatoblastoma with a regimen of vincristine, doxorubicin, and cyclophosphamide. There has been, however, no

TABLE 1. Pancreatoblastoma Treated With Chemotherapy With or Without Surgery*

References	Metastases	AFP (ng/ml)	Chemo	Response	Surgery	Consol.	Outcome
13	N	2,080	THP-ADM/CDDP	PR	Total resection	None	NED 16+ mo
14	H, diaphragm	2	CDDP ADR; VCAD/OPEC	PR	Unresect.	ABMT	Exp. 39 mo
15	None	Normal	IV A; CDDP-ADR	PR	Micros. resid.	XRT-40 Gy	NED 40+ mo
15	None	1,280	ACT-CY; VLB-BLEO-DDP	PR	Biopsy-neg.	None	Relapse-nodes. Treated with chemo/XRT. Exp. 36 mo
16	None	?	Initial surg.	?	?	None	Hep. recurrence partial hepatectomy with postopchemo NED 6+ yr
7	H, P peritoneum	10,000	Not specified	PR	Not done	None	Exp. 10 mo
17	N	Normal	Postop, CDDP-VP16	N/A	Initial surgery-microscopic residual	XRT-40 Gy	NED-5+ yr
18, 19	N, H	2,064	CDDP/ADR/VCR/5FU	PR	Part hepatect + primary & LN resection. Microscopic residual in liver	ABMT	NED 4.5+ yrs.

*Abbreviations: THP-ADM = pirarubicin; CDDP = cisplatin; ADR = adriamycin; VCAD = vincristine, cytoxan, adriamycin; OPEC = vincristine, cytoxan, cisplatin, etoposide; ABMT = autologous bone marrow transplant; IV A = ifosfamide, vincristine, actinomycin; ACT = actinomycin D; CY = cytoxan; VLB = velban; BLEO = bleomycin; N = nodes; H = liver; P = pulmonary; XRT = radiation therapy; NED = no evidence of disease; PR = partial remission; N/A = not applicable; LN = lymph nodes.

consistently successful chemotherapeutic regimen reported.

In short, the best chance for cure in pancreatoblastoma would appear to be complete surgical resection, with a possible role for radiation in disease control or palliation. Unresectable disease portends a poor prognosis.

In the case presented here, interpretation of the biopsy pathology was rendered difficult by uncertainty of the location of the primary tumor in the preoperative period. It was thought that the bulk of the neoplasm was in the pancreas, but the possibility of exophytic growth from a primary in the caudate lobe of the liver could not be ruled out with complete assurance before the second surgical intervention. The presence of a solid epithelial tumor, whose pathologic characteristics indicated a "blastomatous" nature, together with the clinical presumption of a pancreatic primary site and the age of the patient, justified the tentative diagnosis of pancreatoblastoma. However, there were features suggestive of hepatoblastoma, such as characteristic epithelial-sinusoidal trabecular histologic pattern, and the presence of canaliculi demonstrated by electron microscopy. This is not a feature recognized in the generally available descriptions of the pathology of pancreatoblastoma [2,17,19,20], as further discussed below.

After biopsy, the patient was started on radiation therapy and 5-FU. Initial clinical response to this modality in our patient was minimal, although there was a marked reduction in the AFP. Since effective chemotherapy for hepatoblastoma does exist [21] and pathologic diagnosis was not clear, the patient was started on multiple courses of CDDP and ADR, which are two of the most active agents used in the treatment of HBL. There was a dramatic response to these agents, with marked reduction of the mass on CT scan, a 10-fold reduction in alpha-feto-protein levels, and resolution of the lucent lesions seen in the liver. Following the postchemotherapeutic surgical intervention (3 months after biopsy), it became clear that the tumor had originated within the pancreas and had no relationship to the liver.

The epithelial, "liver-like" appearance was retained in some areas of the excised primary tumor, thus emphasizing the "*histogenetic kinship*" of the blastomas primary to the liver and pancreas. Previous reports on the pathology of pancreatoblastoma have not pointed out the possibility of diagnostic confusion with hepatoblastoma. Our patient's tumor did not conform with the recognized histopathology of HBL, nor are there any documented examples of true hepatoblastoma arising within the pancreas [23]. Both of these eventualities, however, seem possible when one bears in mind the close embryologic relationship of these two organs. The embryonic hepatic diverticulum and the dorsal pancreas trace a common origin in the foregut. Two further diverticula originate

from the lower aspect of the hepatic diverticulum; one destined to become the gallbladder and cystic duct, the other the ventral pancreas. The adult pancreas thus originates from two embryonic formations, the dorsal and ventral diverticula, which join each other to form the completed organ [23]. Moreover, there is experimental evidence that pancreatic ductal cells, at least in rodents, are able to transform into hepatocytes [24]. This phenomenon, called "transdifferentiation," has been studied extensively in hamsters and rats, leaving no doubt that pancreatic ductular epithelium can give rise to cells with all the morphologic, functional, and biochemical attributes of hepatocytes, including the presence of "liver-specific" protein markers [24,25]. Conversely, the origination of a pancreatoblastoma in the liver is theoretically possible, given the well-documented occurrence of pancreatic tissue in the liver [26], either by heterotopia or metaplasia.

Intriguing similarities exist between pancreatoblastoma and hepatoblastoma. Hepatoblastoma occurs in association with the Beckwith-Wiedemann syndrome (exomphalos-macroglossia-gigantism, or EMG), as do some other embryonal tumors. There are reports in the literature of pancreatoblastoma occurring in patients with EMG [5,6]. Some authors have speculated that chromosomal abnormalities found in certain patients with EMG, a loss of heterozygosity at chromosome 11 band p13, has been linked with development of rhabdomyosarcoma and hepatoblastoma [28]. Elevation in the serum AFP, another characteristic feature of hepatoblastoma, was present in our patient. Other cases in the literature have demonstrated this marker to be elevated in patients with pancreatoblastoma [7,8], but it is not a universal finding occurring in ~25% of patients [28], and does not appear to be correlated with response or outcome. It has been reported that the raised AFP in pancreatoblastoma is of the yolk sac type, differing from that of hepatoblastoma [29]. This distinction was not determined in our patients.

These considerations have practical relevance, since they are grounds to predict that therapy effective against hepatoblastoma [21] also may be effective against some "blastomas" of the pancreas in contrast to their lack of efficacy in adult pancreatic carcinoma, which probably represents a very different disease entity. Although tumors in adult medicine are generally treated primarily by site of origin, in pediatrics it is common to treat according to histology. Thus extrarenal Wilms' tumor is treated similarly to its intrarenal counterpart, and extraosseous osteogenic sarcoma is treated as the skeletal tumor. Cisplatin as a single agent has no efficacy against pancreatic carcinoma in adults. Doxorubicin and various anthracycline analogues have demonstrated some objective effect in adult disease, but none have shown dramatic efficacy. Combination chemotherapy fails to demonstrate any sig-

nificant benefit in adults, although combinations of the two agents used in this patient have not been studied extensively [12]. Nonetheless, these agents proved very effective as therapy for pancreatoblastoma in our patient. The role of radiation therapy (XRT) and 5 FU was not clear in this case. The initial lack of tumor shrinkage by palpation combined with our interest in trying therapy effective in HBL prompted an early change in therapy. However, XRT and 5FU have also been successfully used in the treatment of hepatoblastoma [21]. Although there appeared to be a dramatic response to CDDP and ADR, the initial therapy also might have contributed to this observed response, particularly in view of the 10-fold decrease in AFP prior to initiation of CDDP and ADR.

Our patient presented with a massive, inoperable, pancreatic blastomatous malignancy for which nonsurgical therapy has been notoriously unrewarding in the past. The tumor was rendered operable by a therapeutic approach of proven efficacy against hepatoblastoma, and the child was rendered free of disease.

Unfortunately, this child's tumor recurred at the site of initial metastatic lesions in the absence of recurrence at the primary site. These lesions were not initially treated with either resection or irradiation therapy. Patients in the literature who have had a successful outcome have all undergone total resection of tumor and/or local irradiation therapy either primarily or after initial tumor shrinkage with chemotherapy. Perhaps related to this, the extent of disease at diagnosis also may impact on survival, as most surviving patients have had only regional disease (local with or without regional nodal involvement).

CONCLUSIONS

It appears that total eradication of all tumor is required for cure. It is suggested by these cases that consolidation with megadose chemotherapy and involved field RT followed by autologous stem cell rescue may be successful when tumor cannot be totally eradicated by other modalities. Pancreatoblastoma is a chemotherapy responsive tumor and should be approached like other pediatric tumors with an aggressive combined modality approach.

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REFERENCES

- Gonzalez-Crussi F, Upton MP, Maurer HS: Hepatoblastoma: Attempts at characterization of histologic subtypes. *Am J Surg Pathol* 6:599-612, 1982.
- Horie H, Yano Y, Kotoo Y, Mowa A: Morphogenesis of pancreatoblastoma, infantile carcinoma of the pancreas. Report of two cases. *Cancer* 39(1):247-254, 1977.
- Nagaraj H, Polk HC Jr: Pancreatic carcinoma in children. *Surgery* 95(4):505, 1984.
- Griffin BR, Wisbeck WM, Schaller RT, Benjamin DR: Radiotherapy for locally recurrent infantile pancreatic carcinoma (pancreatoblastoma). *Cancer* 60(8):1734-1736, 1987.
- Drut R, Jones MC: Congenital pancreatoblastoma in Beckwith-Wiedemann syndrome: An emerging association. *Pediatr Pathol* 8(3):331-339, 1988.
- Koh TH, et al: Pancreatoblastoma in a neonate with Wiedemann-Beckwith syndrome. *Eur J Pediatr* 145(5):435-438, 1986.
- Iseki M, et al: Alpha-fetoprotein producing pancreatoblastoma, a case report. *Cancer* 57(9):1833-1835, 1986.
- Morohoshi T, Sagawa F, Mitsuya T: Pancreatoblastoma with marked elevation of serum alpha-fetoprotein: An autopsy case report with immunocytochemical study. *Virchows Arch [A]* 416(3):265-270, 1990.
- Camprodon R, Quintenilla E: Successful long term results with resection of pancreatic carcinoma in children: Favorable prognosis for an uncommon neoplasm. *Surgery* 95(4):420-426, 1984.
- Tsukimoto I, et al: Pancreatic carcinoma in children in Japan. *Cancer* 31(5):1203-1207, 1973.
- Taxy JB: Adenocarcinoma of the pancreas in childhood: Report of a case and a review of the English language literature. *Cancer* 37(3):1508-1518, 1976.
- Brennan MF, Kunsella T, Friedman M: Cancer of the pancreas. In DeVita VT, Hellmans-Rosenberg, SA (eds): "Cancer: Principles and Practice of Oncology," 3rd ed. Philadelphia: Lippincott, 1989.
- Inomata Y, Nishizawa T, Takasa H, et al: Pancreatoblastoma resected by delayed primary operation after effective chemotherapy. *J Pediatr Surg* 27(12):1570-1572, 1992.
- Eden OB, Shaw MP: Letter to the Editor: Chemotherapy for pancreaticoblastoma. *Med Pediatr Oncol* 20(4):357-359, 1992.
- Vannier JP, Flamant F, Hemet J, et al: Pancreatoblastoma: response to chemotherapy. *Med Pediatr Oncol* 19(3):187-191, 1991.
- Grosfeld JL, Vane DW, Rescorla FJ, et al: Pancreatic tumors in childhood: Analysis of 13 cases. *J Pediatr Surg* 25(10):1057-1062, 1990.
- Silverman JR, Holbrook CT, Pories WJ, et al: Fine needle aspiration cytology of pancreatoblastoma with immunocytochemical and ultrastructural studies. *Acta Cytologica* 34(5):632-640, 1990.
- Stephenson CA, Kletzel M, Seibert JJ, Glasier CM: Pancreatoblastoma: MR appearance. *J Comput Assist Tomogr* 14(3):492-494, 1990.
- Buchino JJ, Castello FM, Nagaraj HS: Pancreatoblastoma: A histochemical and ultrastructural analysis. *Cancer* 53:963-969, 1984.
- Ichyima K, Akaishi K, Toyanda N, et al: Carcinoma of the pancreas with endocrine component in child: A case report. *Am J Clin Pathol* 83:95-100, 1985.
- Greenberg M, Filler RM: P.A. Pizzo, D.G. Poplack (eds): "Hepatic Tumors: Principles and Practices of Pediatric Oncology." Philadelphia: Lippincott, 1989, pp. 569-580.
- Gonzalez-Crussi F, Upton MP, Mauer HS: Hepatoblastoma: Attempt to characterization of histologic subtypes. *Amer J Surg Pathol* 6:559-612, 1982.
- Harrison RG: The foregut. In: "A Textbook of Human Embryology" chap. 11. Oxford: Blackwell, 1959, pp. 99-100.
- Rao MS, Scarpelli DG, Reddy JK: Transdifferentiated hepatocytes in rat pancreas. *Curr Topics Devel Biol* 20:63-78, 1986.
- Makino T, Usuda N, Rao S, Reddy JK, Scarpelli DG: Transdifferentiated

- entiation of ductular cells into hepatocytes in regenerating hamster pancreas. *Lab Invest* 62(5):552–561, 1990.
26. Wolf HK, Burchette JL, Garcia JA, Michalopoulos G: Exocrine pancreatic tissue in human liver: A metaplastic process? *Am J Surg Pathol* 14(6):590–595, 1990.
27. Koufos A, et al: Loss of heterozygosity in three embryonal tumors suggest a common pathogenetic mechanism. *Nature* 316:330–334, 1985.
28. Horie A, Haratake J, Jimi A, et al: Pancreatoblastoma in Japan, with differential diagnosis from papillary cystic tumor (ductuloacinar adenoma) of the pancreas. *Acta Pathologica Japonica* 37(1): 47–63, 1987.
29. Tsuchida Y, Kaneko M, Fukui M, et al: Three different types of alpha-fetoprotein in the diagnosis of malignant solid tumors: Use of a sensitive lectin-affinity immunoelectrophoresis. *J Pediatr Surg* 24(4):350–355, 1989.